## Remarks

Applicants thank the Examiner for the detailed office action of December 16, 2004 and the in-person interview on January 25, 2005.

With entry of this Amendment and Response, claims 69-78, 82-87, 91-93, and 95-98 are pending in the present application. Claims 79-81, 88-90, and 94 are cancelled without prejudice. Applicants reserve the right to represent the cancelled subject matter in one or more continuation applications. Claims 69-73, 83, 86, 87, and 91-93 are amended. The amendments to the claims are supported throughout the specification, including but not limited to page 4, line 15-22, and lines 23-35, page 5, lines 10-13, page 7, lines 5-18, and page 3, lines 9-17.

Amendment of claims 69 and 92-93 for manufacturing for use in a topical application is supported by the specification, for example, but not limited to, page 8, line 24 to page 9, line 12.

Claim 91 has been amended to claim an extract of liana Uncaria tomentosa and special extracts thereof, but they be on the basis of original specification as filed pages 18 and 19 which disclose an aqueous-alcohol extract, an aqueous extract, and an aqueous glycolic extract, and page 24, lines 13-16, which discloses an aqueous, glycolic or alcoholic extract of liana Uncaria tomentosa.

Claims 95-98 are added. New claims 95 and 96 are supported throughout the specification, including but not limited to page 7, lines 28-34, and new claims 97 and 98 are supported throughout the specification, including but not limited to page 5, lines 17-22 and page 6, lines 23-29.

## Interview of January 25, 2005

Applicants thank the Examiners for their discussion and language suggestions for resolving the §112 issues presented in the Office Action of December 12, 2004.

## Claim Rejections - 35 U.S.C. § 112

Claims 86-90 are rejected under 35 U.S.C. §112 ¶1 for lack of enablement regarding screening for identification of isolated, individual compounds. Applicants respectfully disagree. The claims, as amended, are directed to a screening method for selecting a compound or extract demonstrating LPL inhibition. The screening method does not identify the active moiety within

an extract, but rather determines if the desired LPL inhibition activity is present. This determination is readily preformed on either isolated compounds or extracts in view of the specification. For example, support is provided, but not limited to, page 3, lines 1-8; page 4, lines 15-23; page 14, lines 5-10; pages 18 and 19; and pages 24, lines 13-16 of the specification. Removal of the enablement rejection is respectfully requested.

Claims 87 -89 are rejected for lack of enablement for screening all possible liana in the claimed method. Applicants respectfully disagree. The specification teaches how to obtain an extract of natural product, one example being liana Uncaria tomentosa, and screen the extract for inhibition of LPL. Creation of extracts for screening in the present method is enabled by the description provided at page 14-15 indicating that the procedure for creating an extract of liana on page 18, lines 10-25 was also used to form the extracts whose LPL inhibition results appear on page 15 in Table 3. The specific examples of liana Uncaria tomentosa and St. John's Wort are presented as specific examples of extracts demonstrated by the screening method to inhibit LPL activity. Therefore, claimed screening method is demonstrated in the specification as being operative for its use, which is to select compounds or extracts having LPL inhibiting activity.

In the rejection of claims 87-89 for lack of enablement that one would not know how to identify suitable species of liana that would be potentially active substances for the claimed assay. Applicants respectfully disagree. The claims are directed to a screening method for determining if a compound or extract has LPL inhibiting activity. Therefore, the claimed method provides teaching for one to screen species of liana or other extracts for LPL inhibition activity. Applicants respectfully request the rejection for lack of enablement be withdrawn.

Various rejections of claims 69-94 are also made under 35 U.S.C. §112, ¶2.

Claim 69 is rejected for omitting essential steps. Claims 69 and 92-94 are rejected because "comprising a test of the capacity of the screen compound to inhibit LPL" is confusing and "field of lipolysis" is indefinite. The claims are amended to address these rejections.

Claims 70-73 and 83 are amended to overcome objections as regards omission of essential steps. In particular these claims recite a step indicating how one correlates the effect of tested compounds with the goal of each claim.

Claim 70 is rejected for "potentially active substance" as being unclear. The term "potentially active substance" has been canceled of the claims.

Claim 88 is rejected for lack of antecedent basis for "said extract." Amendment of claim 69 to include extracts has alleviated this rejection.

Claim 92 is amended to clarify "diminishing or slowing down the fatty deposits."

Applicants respectfully submit that the rejections under §112 have been addressed by amendment of the claims and the remarks presented above. Therefore, the Applicants respectfully request reconsideration and withdraw of the rejection of claims 69-94 under 35 U.S.C. § 112.

## Claim Rejections - 35 U.S.C. § 102

Claims 69 and 92 are rejected under 35 U.S.C. §102(b) as being anticipated by *Cook et al.* (U.S. 5,855,917).[1] Applicants respectfully traverse.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claims 69 and 92 of the present invention are drawn to a screening method for identifying compounds or extracts that inhibit LPL for use in topical applications, such as cosmetics. The claimed screening methods utilize a cell-free *in vitro* test of LPL inhibition.

Cook does not describe each and every element of claims 69 and 92. Cook describes treatment of preadipocytes with conjugated eicosadionic acid and assessment of heparin-releasable lipoprotein lipase activity. Cook does not teach the cell-free *in vitro* test as claimed. Furthermore, Cook does not teach or suggest a general method for screening for LPL activity in compounds or extracts for use in topical applications. Therefore, Cook does not teach each and every element of claims 69 and 92. Applicants respectfully request withdrawal of the §102(b) rejection of claims 69 and 92 in view of Cook.

[1] Please note the Office Action of 12/16/2004 indicated Cook et al. as patent number 5,244,798 (Takeda et al.) on page 6. The correct number for Cook was later indicated at page 7.

Claims 69 and 88 are rejected under 35 U.S.C. §102(e) as being anticipated by Halvorsen et al. (US 2001/0041708). Applicants respectfully traverse.

Claims 69 and 88, as amended, are drawn to a screening method for identifying compounds or extracts that inhibit LPL for use in topical applications, such as cosmetics. The claimed screening methods utilize a cell-free *in vitro* test of LPL inhibition. Claim 88 is further directed to a glycolic aqueous extract of liana Uncaria tomentosa.

Halvorsen does not describe each and every element of claims 69 and 88. Halvorsen teaches a method for reducing cellulite by administering 10-trans, 12-cis linoleic acid. Halvorsen's method is directed towards increasing lypolysis (by HSL –hormone-sensitive lipase) of fatty deposits carried within adipocytes, thereby converting the stored fat into free fatty acids (¶0028). In contrast, the claimed method is directed to LPL inhibition thereby inhibiting breakdown of blood-borne triacylglycerols and very low density lipoproteins (VLDL) blocking entry of free (non-esterified) fatty acids into adipocytes for subsequent storage (specification page 3, lines 24-35).

Furthermore, Halvorsen relies on testing methods utilizing whole cells, e.g., adipocytes. Halvorsen does not teach the cell-free *in vitro* screening method for determining LPL inhibition of the claimed method. Halvorsen does not describe extracts, such as extract of liana Uncaria tomentosa. Therefore, Halvorsen does not teach all the elements of claims 69 and 88. Applicants respectfully request withdrawal of the §102(b) rejection of claims 69 and 88 in view of Halvorsen et al.

Claim 93 is rejected under 35 U.S.C. §102(b) as being anticipated by Carroll et al. (Lipids, 1982, Vol. 27, p.4). Applicants respectfully traverse.

Claim 93 is drawn to a screening method for identifying compounds or extracts that inhibit LPL for use in topical applications, such as cosmetics, for increasing blood microcirculation. The claimed screening method utilizes a cell-free *in vitro* test of LPL inhibition.

Carroll does not teach all the elements of claim 93. Carroll characterizes the sensitivity of diacylglycerol (DAG) lipase to the inhibitor, U-57,908, as compared to the sensitivity lipoprotein lipase in lysates of cardiac myocyte cells and heparin-treated cardiac myocytes. The assay performed in Carroll uses cellular lysates or whole myocyte cells and tracks the enzyme

kinetics using radioactive triolein. Carroll does not describe a screening method for identifying compounds or extracts that inhibit LPL for use in topical applications for increasing blood microcirculation. Furthermore, Carroll does not describe the cell-free *in vitro* screening method of claim 93. Applicants respectfully request withdrawal of the §102(b) rejection of claim 93 in view of Carroll.

## Claim Rejections - 35 U.S.C. § 103

Claims 70-86 are rejected under 35 U.S.C. § 103 as obvious in view of the combination of:

Cook et al. (U.S. 5,855,917)
Wagle et al. (U.S. 6,326,396)
Takahashi et al. (U.S. 5,955,072)
Takeda et al. (U.S. 5,244,798)
Vainio et al. (1982)
Cheng et al. (1990)
Carroll et al. (1992)
Bensadoun et al. (1974)
NEFA-C kit from Wako & instructions
Kikuchi et al. (U.S. 4, 301, 244)

Applicants respectfully traverse.

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. MPEP §2141.

The office action relies on the teaching in *Cook et al.* of an LPL assay and the other references as "supporting references" demonstrating "a number of compounds capable of inhibiting LPL". The supporting references are employed by the office action to address technical aspects of the assay in the dependent claims. Applicants respectfully disagree the

screening method of the present invention is obvious in view of the combination of cited references.

Independent claim 70 is directed to an *in vitro* cell-free screening method for identifying a compound or extract for manufacturing a topical composition for inhibiting lipoprotein lipase (LPL). Claims 71-86, dependent thereon, are directed likewise.

In contrast to the claims, *Cook et al.* is directed to compositions for oral administration to control body fat or body weight in animals. (Col. 4, line 36 and Col.5, lines 12-20.) Cook teaches inhibition of heparin-released lipoprotein lipase by treatment of adipocyte cells with eicosadienoic acid. (See Col.3, Example 3.) Cook does not teach a screening assay, but instead demonstrates inhibition of lipase activity by eicosadionic acid in preadipocyte cells and pigs. Cook does not disclose the claimed cell-free *in vitro* screening method for identifying active compounds and extracts for use in manufacturing a topical composition for limiting storage of triglycerides.

References such as *Wagle et al.* and *Takahashi et al.* do not overcome the deficiencies of Cook. Wagle also utilizes adipocyte cells and animal testing. However, Wagle is directed to a different lipase, i.e. hormone-sensitive lipase, and consequently does not add to the teachings of Cook. Takahashi also describes testing for LPL activity using adipocyte cells. In combination, Cook, Wagle and Takahashi do not teach all the limitations of the claims. Furthermore, Applicants assert there is no motivation to combine the above teachings of Cook, Wagle and Takahashi with the additional cited references.

Another group of references, *Takeda et al.*, *Kikuchi et al.*, and the *NEFA C Kit* are generally directed to analysis of free fatty acids or triglycerides. Takeda teaches utilizing a LPL ortholog from streptomyces (bacteria) in a reagent for measuring triglycerides in blood samples. Kikuchi teaches a reagent for analysis of free fatty acids. The NEFA C Assay Kit is for the quantitative determination of free fatty acids in serum or plasma.

The remaining references, *Bensadoun et al.* (1974), *Vainio et al.* (1982), *Cheng et al.* (1990), and *Carroll et al.* (1992) are directed to *in vitro* studies of the enzyme kinetics of lipoprotein lipase. Bensadoun describes purification and characterization of LPL from adipose tissue. Vainio, Cheng, and Carroll study the rate and mechanism of enzyme catalysis by which LPL converts triglycerides into fatty acids and glycerol. Vainio and Cheng study the rate and mechanism of enzyme catalysis by which LPL converts triglycerides into fatty acids and glycerol.

Cheng is directed to characterization of inhibition of LPL activity form cardiac myocytes. Vainio uses benzene-boronic acid to study the mechanism of enzyme catalysis. These kinetic studies utilize radioactive-labeled substrate to measure substrate conversion by LPL.

The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). Furthermore, knowledge in the art is not sufficient to establish obviousness without some objective reason to combine the teachings of the references. *Ex Parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

Cook and Takahashi use adipocyte cells and animal testing to test compounds for LPL activity. Cook and Takahashi do not provide any statements that those methods are unsatisfactory for their purpose nor is any suggestion made for modification to provide a screening method, such as is claimed. Use of adipocyte cells and animal testing is common in assessing compounds for biological activity because of a general premise that in vivo results are better predictors of in vivo activity than is *in vitro*. Bensadoun, Vainio, Cheng, and Carroll are not directed to screening methods for discovery of new extracts or compounds with LPL inhibitory activity. Therefore, there is no motivation or guidance to adapt the in vivo methods of Cook and Takahashi with the *in vitro* characterization of enzyme kinetics of Bensadoun, Vainio, and Cheng.

In addition to combining the disparate teachings of Cook, Takahi, Bensadoun, Vainio, Cheng, and Carroll, a further combination with Kikuchi or the Nefa C kit is proposed. Kikuchi and the Nefa C kit teach the measurement of free fatty acids in blood or serum. The colorimetric methods of Kikuchi and the Nefa C kit are for making quantitative determinations, and therefore are not compatible with the analysis of Bensadoun, Vainio, Cheng and Carroll, wherein radioactive substrate was used to provide kinetic information, such as the rate of substrate conversion over time.

The combination of cited references fails to teach the claimed cell-free *in vitro* screening method. Furthermore, none of the cited references provides motivation for combination and selective substitution or modification of particular aspects within the cited combination sufficient to render the claimed cell-free, *in vitro* screening method obvious.

Claims 69-88 and 91 are rejected under 35 U.S.C. § 103 as obvious in view of the combination of:

Cook et al. (U.S. 5,855,917)
Wagle et al. (U.S. 6,326,396)
Takahashi et al. (U.S. 5,955,072)
Takeda et al. (U.S. 5,244,798)
Vainio et al. (1982)
Cheng et al. (1990)
Carroll et al. (1992)
Bensadoun et al. (1974)
NEFA-C kit from Wako & instructions
Kikuchi et al. (U.S. 4, 301, 244)
and further in view of Halvorsen et al. (US 2001/0041708).

Applicants respectfully traverse.

Claims 69, and 87-88 dependent thereon, are drawn to a screening method for identifying compounds or extracts that inhibit LPL for use in topical applications, such as cosmetics. Claim 70, and claims 71-86 dependent thereon, are directed to an *in vitro* cell-free screening method for identifying a compound or extract for manufacturing a topical composition for inhibiting lipoprotein lipase (LPL). The claimed screening methods utilize a cell-free *in vitro* test of LPL inhibition.

Claims 69-88 and 91 are not rendered obvious by the cited combination in view of the comments provided above, incorporated here by reference.

The office action adds *Halvorsen et al.* to the previous combination of references, to teach the extracts such as St. John's wort can be tested for slimming activity. Applicants respectfully disagree.

The further combination with *Halvorsen et al.* does not rectify the deficiencies of combination of references. Halvorsen does not teach the cell-free *in vitro* screening method of the claims. In contrast, Halvorsen is directed to decreasing lipogenesis by administering conjugated linoleic acid(CLA). The compounds of Halvorsen have effect on hormone-sensitive lipase but not on LPL as required by the present claims. See, for example, paragraphs [0135]-[0136] and Example 5b at paragraph [0102], and further characterized at the end of paragraph [0143] demonstrating that CLA compounds did not impact lipolysis. Furthermore, Halvorsen teaches assay methods using preadipocytes (see, for example, paragraphs [0108] and [0112]), in contrast to the cell-free *in vitro* method of the claims.

The above combination does not teach the claimed cell-free *in vitro* screening method for identifying a compound or extract for manufacturing a topical composition for inhibiting

lipoprotein lipase (LPL) activity. Furthermore, there is a lack of motivation to modify the cited references to render the claimed screening method obvious.

Applicants respectfully request withdrawal of the 35 USC § 103 rejection of claims 69-88 and 91.

New claims 95-98 are related in scope to claims 69, 70, 92, 93 or 94, so that these claims are deemed to be allowable on the same basis.

## Conclusion

In view of the amendments and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested for claims 69 to 98. The Examiner is invited to contact Anne Murphy, PTO Reg. No. 54,327 at 612.371.5267 if the Examiner believes a telephone conference would further prosecution of the above application.

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